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Hypogonadism in male outpatients with sarcoidosis

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Summary
Hypogonadism is assumed to be present in sarcoidosis. Nevertheless, a comparison of circulating sex hormone concentrations of male sarcoidosis patients with those of healthy men has never been done. Moreover, it remains unknown if hypogonadism may contribute to a reduced muscle function, exercise intolerance, diminished vitality and depressed mood in male sarcoidosis patients.
Pulmonary function, muscle function, exercise tolerance, vitality, mood, circulating sex hormone concentrations and C-reactive protein were assessed in 30 male sarcoidosis patients and 26 age-matched men with a normal pulmonary function.
On average, patients had a restrictive pulmonary function, worse inspiratory and quadriceps muscle function, functional exercise intolerance, diminished vitality, depressed mood and increased systemic inflammation. Moreover, patients had significantly lower circulating (free) testosterone concentrations, while circulating sex hormone-binding globulin tended to be lower ($p = 0.0515$). Circulating gonadotrophin concentrations were comparable. Non-significant relationships were found between sex hormones, clinical outcomes and C-reactive protein in patients with sarcoidosis.
A significant number of male outpatients with sarcoidosis (46.7%) had low circulating testosterone concentrations, which was most probably caused by hypogonadotrophism. The clinical relevance of hypogonadism in male outpatients with sarcoidosis, however, remains currently unknown. Indeed, poor inspiratory and quadriceps muscle function,

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exercise intolerance, diminished vitality and depressed mood were not related to hypogonadism in these patients.

Introduction

Sarcoidosis is a heterogeneous multi-system disorder of unknown aetiology with varying presentation of symptoms, which often presents with bilateral hilar lymphadenopathy and pulmonary infiltration.[1] Respiratory and skeletal muscle function,[2,3] exercise tolerance,[3,4] symptoms of fatigue,[3,5,6] vitality[3,7–10] and mood status[3,7,10] have been shown to be worse in comparison with healthy age-matched control subjects and appear, at least in part, to be interrelated.[3] These clinical features can be the resultant of the disease itself, but can also be secondary to persistent debilitating clinical complaints and to the pharmacological treatment of sarcoidosis.[1,3]

Skeletal muscle weakness, fatigue and depression have been shown to be partly related to low circulating (free) testosterone in male outpatients with chronic diseases (i.e. human immunodeficiency virus, chronic obstructive pulmonary disease and depressive illness) and in aging healthy men.[11–16] Circulating testosterone concentrations appear also to be low in male outpatients with sarcoidosis.[17] Nonetheless, in the latter study a healthy control group was lacking, patients were mostly African American and one patient was thought to have neurosarcoidosis.[17] Moreover, the aforementioned relationships have never been studied in male outpatients with sarcoidosis.

Although a direct comparison of circulating gonadotrophins concentrations of male sarcoidosis patients with those of middle-aged healthy men has never been done, hypogonadism in sarcoidosis can be of primary testicular dysfunction and/or a dysfunctioning hypothalamus-pituitary-gonadotrophic axis.[17,18] In addition, hypogonadism can be caused by systemic inflammation[15] or can be an inconvenient side effect of the treatment with oral corticosteroids.[19] The role of oral corticosteroids in the development of hypogonadism, however, may be less prominent than expected.[15,17,20] A cross sectional study was therefore undertaken to investigate two questions:

- Are circulating levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, sex hormone-binding globulin (SHGB) and free testosterone of male outpatients with sarcoidosis significantly different from those of healthy middle-aged men?
- What is the relationship between circulating (free) testosterone concentrations and respiratory and skeletal muscle function, 6-min walking distance, vitality, depression, systemic inflammation and mean daily dose of corticosteroids in men with sarcoidosis?

Material and methods

Study subjects and design

Forty-six consecutive male outpatients with sarcoidosis visited the outpatient consultation of the Interstitial Lung Diseases Unit of the University Hospital Gasthuisberg in Leuven (Belgium) and were asked to participate in the present study. Sixteen patients were reluctant to participate. Consequently, pulmonary function, respiratory and skeletal muscle function, functional exercise capacity and circulating levels of several hormones of the pituitary-gonadal axis were determined in 30 consenting male outpatients. Moreover, systemic inflammation, vitality, depression and the seriousness of self-reported co-existing comorbidities were determined as described below. Finally, based on their chest radiograph, the sarcoidosis patients were classified according to Scadding[21]: stage 0, no lung involvement; stage 1, hilar enlargement alone; stage 2, hilar enlargement plus interstitial lung disease; stage 3, interstitial lung disease alone; and stage 4, lung fibrosis.

Sarcoidosis had been diagnosed a median of 3 years previously (interquartile range, IQR: 3–9) according to the latest ATS/ERS/WASOG statement on sarcoidosis.[1] Fourteen patients received oral corticosteroids in the 6-month period before testing at a mean dose of 1.8–32.0 milligram of oral methylprednisolone equivalents per day. The results of the consenting outpatients with sarcoidosis were compared to those of 26 healthy middle-aged men (Table 1) who were not actively participating in sporting activities. Three students of the authors' faculty recruited the latter group among relatives and friends.

The present design was in accordance with World Medical Association declaration of Helsinki.[22] The ethics committee of the University Hospitals Leuven granted approval for the present survey (local reference: ML2914). Except for one African Belgian patient, all participants were of white ethnic origin. All patients and control subjects gave oral and written informed consent. Muscle function of seven sarcoidosis patients[3] and gonadal status of four middle-aged control subjects[15] have been published elsewhere. Moreover, for 14 male patients the present assessments were obtained at baseline of the *EXTRAS* study.[23]

Methods

Venous blood was drawn from supine participants between 08.30 and 09.00 A.M. before functional testing. Circulating levels of FSH, LH, testosterone, SHBG and free testosterone were determined or calculated as described previously by Van Vliet and colleagues in an online supplement.[15] In addition, C-reactive protein (CRP), as a marker of systemic inflammation, has been assessed.[24]

Forced expiratory volume in the first second, forced vital capacity, total lung capacity and carbon monoxide transfer factor were measured according to the guidelines of the European Respiratory Society.[25] In addition, maximal inspiratory mouth pressure sustained for 1 s, isometric quadriceps peak torque and the distance walked in 6 min were assessed as described previously by Spruit and colleagues in an online supplement.[3] In addition, reference values of

Table 1 Demographics.

	Sarcoidosis ($n = 30$)	Healthy ($n = 26$)	*p-value*
Age, years	43.6 (2.1)	43.6 (2.8)	0.9958
BMI, kg/m^2	26.5 (0.8)	25.7 (0.6)	0.2968
FEV_l, l	3.29 (0.18)	3.94 (0.16)	0.0104
FEV_l, % pred	84.8 (3.8)	100.4 (2.8)	0.0020
FVC, l	4.44 (0.19)	5.13 (0.19)	0.0164
FVC, % pred	93.9 (3.3)	106.8 (2.8)	0.0062
TLC, l	6.29 (0.19)	7.25 (0.19)	0.0014
TLC, % pred	89.2 (2.4)	101.0 (2.5)	0.0034
TL,CO, mmol/min/Kpa	8.17 (0.38)	10.45 (0.40)	0.0003
TL,CO, % pred	75.8 (3.2)	95.4 (2.5)	0.0001
Smoking, c/f/n	5/3/22	6/1/19	0.5980
Pack years*	9 (5–18)	15(10–25)	0.1462
Scadding, I–IV	8/15/5/2	–	–

Values are expressed as mean (SE), except for Scadding's chest radiograph scores [21] and smoking status (c = current; f = former; n = never, absolute numbers), and for number of packyears and Charlson index [31] (median (IQR)). m = meters; BMI = body mass index; kg m^{-2} = body weight per square height; FVC = forced vital capacity; l = liters; % predicted = percent of the predicted value; FEV1 = forced expiratory volume in the first second; TLC = total lung capacity; TL,CO = transfer factor for carbon monoxide of the lungs; *Packyears have been calculated for eight current or former smoking patients and seven current or former smoking control subjects.

Rochester and Arora,[26] Decramer and colleagues[27] and of Trooster and colleagues[28] have been used to calculate the predicted values, respectively.

The domain *vitality* of the Medical Outcomes Study 36-Item Short-Form Health Survey,[29] and the domain *depression* of the Hospital Anxiety and Depression Scale[30] were used to assess vitality and depression, respectively. Vitality scores could range from 0 (worst) to 100 (optimal), while depression scores could range from 0 (optimal) to 21 (worst).

Self-reported co-existing comorbidities have been classified using the Charlson index, which is a simple weighted index that takes into account the number and the seriousness of comorbid disease.[31]

Statistical analyses

Results are presented as mean (standard error of the mean, SE) or as median (IQR), as appropriate. A two-tailed unpaired *t*-test (continuous), a Mann–Whitney *U* test or a chi square test (binomial) was used to determine differences between sarcoidosis patients and healthy control subjects. Spearman rank correlation (r_s) has been used to determine relationships between circulating (free) testosterone concentrations and clinical outcomes in the patients. In addition, a partial correlation was calculated between testosterone and quadriceps peak torque (Newton-meters) after controlling for age, body weight and height. *A priori*, a two-sided level of significance was set at $p \leqslant 0.05$.[32]

Results

Characteristics

Patients with sarcoidosis had a statistically significant worse pulmonary function (Table 1), respiratory and skeletal muscle function and functional exercise capacity than healthy peers (Table 2). In addition, patients had worse median scores for vitality and depression (Table 2), and increased circulating CRP concentrations (Table 3). Age, body mass index and smoking status were comparable between the two groups (Table 1).

Table 2 Physical function, vitality and depression.

	Sarcoidosis (n = 30)	Healthy (n = 26)	*p-value*
PImax, cmH_2O	−103.2 (4.5)	−126.0 (5.4)	0.0019
PImax, % pred	84.8 (3.7)	103.1 (3.7)	0.0010
QPT, Nm	167.7 (8.6)	207.7 (8.9)	0.0023
QPT, % pred	73.4 (3.9)	92.3 (3.2)	0.0005
6 MWD, m	622 (25)	782 (23)	0.0001
6 MWD, % pred	78.3 (3.1)	98.1 (2.1)	0.0001
Vitality, points	40 (20–55)	80 (65–90)	0.0001
Depression, points	8 (3–10)	0 (0–2)	0.0001

Values are expressed as mean (SE), except for vitality and depression (median (IQR)). PImax = maximal inspiratory mouth pressure; QPT = quadriceps peak torque; 6 MWD = 6-min walking distance; vitality scores can range from 0 points (worst) to 100 points (optimal); depression scores can range from 0 points (optimal) to 21 points (worst). $n = 29$ outpatients with sarcoidosis for vitality and depression.

Hormones of the pituitary–gonadal axis

Median circulating gonadotrophins concentrations were similar between patients and healthy control subjects. In addition, male outpatients with sarcoidosis had significantly

Table 3 Systemic inflammation and gonadal status.

	Sarcoidosis ($n = 30$)	Healthy ($n = 26$)	*p-value*
CRP, mg/l	1.8 (1.0–4.1)	1.0 (1.0–1.0)	0.0086
FSH, mIU/ml	3.6 (2.7–6.6)	4.3 (3.1–6.3)	0.5818
LH, mIU/ml	2.9 (2.4–3.6)	3.4 (2.5–4.9)	0.1598
TST, ng/dl	321 (245–404)	426 (375–475)	0.0014
SHBG, μg/dl	0.81 (0.58–1.08)	1.02 (0.79–1.33)	0.0515
Free TST, ng/dl	7.32 (5.48–8.72)	9.25 (7.54–9.87)	0.0062

Values are expressed as median (IQR). FSH = follicle stimulating hormone; LH = luteinizing hormone; TST = testosterone; SHBG = sex hormone-binding globulin.

lower median circulating levels of testosterone and free testosterone than healthy middle-aged men, while circulating SHBG concentrations tended to be lower in the patients (Table 3).

Age was related to circulating levels of SHBG ($r_s = 0.56$, $p = 0.0014$) and free testosterone ($r_s = -0.53$, $p = 0.0025$) in the patients with sarcoidosis. In addition, circulating testosterone concentrations were significantly related to circulating levels of SHBG ($r_s = 0.63$, $p = 0.0002$) and free testosterone ($r_s = 0.81$, $p = 0.0001$).

Oral corticosteroids and sex hormones

Median circulating levels of testosterone and free testosterone did not differ between patients who used oral corticosteroids in the past 6 months ($n = 14$, 284 ng/dl (186–406); and 7.32 ng/dl (4.70–8.95), respectively) and those who did not ($n = 16$, 345 ng/dl (266–401), $p = 0.8843$; and 7.32 ng/dl (6.15–8.42), $p = 0.3286$, respectively). In addition, patients who did not use oral corticosteroids in the past 6 months had significantly lower circulating levels of testosterone ($p = 0.0111$) and free testosterone ($p = 0.0156$) than healthy control subjects.

Co-existing morbidities and sex hormones

Four patients reported one co-existing morbidity on the Charlson comorbity index: diabetes mellitus type 2 ($n = 2$); congestive heart failure ($n = 1$); and mild liver disease ($n = 1$). None of the control subjects reported co-existing morbidities. Consequently, self-reported co-existing morbidities were more prevalent in the sarcoidosis patients compared to healthy peers (χ^2: $p = 0.049$). Patients without self-reported co-existing morbidities had significantly lower median circulating levels of testosterone (316 ng/dl (245–406), $p = 0.0033$) and free testosterone (7.42 ng/dl (5.48–8.95), $p = 0.0275$) than healthy control subjects.

Clinical outcomes and sex hormones

Reduced circulating (free) testosterone concentrations were not significantly related to body mass index, pack years, maximal inspiratory mouth pressure sustained for 1 s, quadriceps muscle force (upper panel of Figure 1), functional exercise intolerance, diminished vitality (lower panel of Figure 1), depressed mood or systemic inflammation in male outpatients with sarcoidosis (Table 4). In addition, no significant relationship has been found between quadriceps peak torque and circulating testosterone levels, after controlling for age, body weight and height ($r = 0.063$, $p = 0.754$).

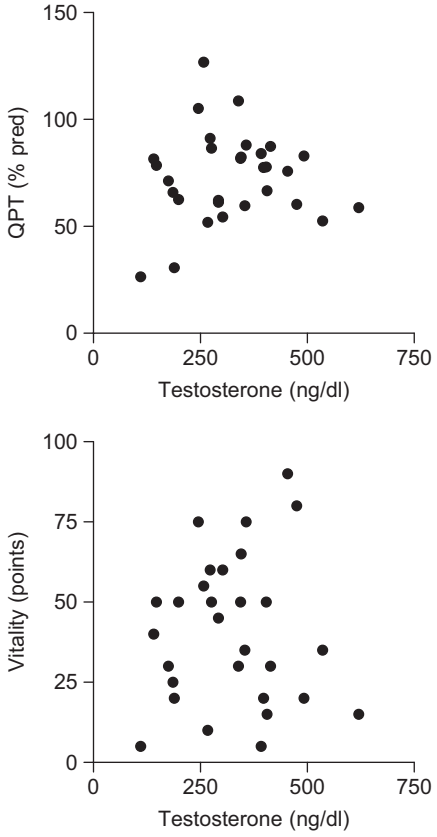

Figure. 1 *Upper panel*: Testosterone (expressed as ng/dl) versus quadriceps peak torque (expressed as a % of the predicted value) in male outpatients with sarcoidosis. *Lower panel*: Testosterone (expressed as ng/dl) versus vitality (expressed in arbitrary units: points) in male outpatients with sarcoidosis.

Discussion

The present study has two novel observations: (1) male outpatients with sarcoidosis had lower median circulating (free) testosterone concentrations than healthy

Table 4 Spearman correlation coefficients between testosterone status and clinical outcomes in male outpatients with sarcoidosis.

	Testosterone (ng/dl)	Free testosterone (ng/dl)
Age, years	−0.08	−0.53*
BMI, kg/m^2	−0.17	−0.20
FVC, % pred	−0.17	−0.20
TL,CO, % pred	−0.02	−0.04
Pack years	0.19	0.14
PImax, % pred	0.09	−0.05
QPT, % pred	0.02	−0.09
6 MWD, % pred	0.04	−0.16
Vitality, points	0.02	−0.14
Depression, points	0.09	0.25
CRP, mg/l	−0.15	−0.30

m = meters; BMI = body mass index; kg m^{-2} = body weight per square height; FVC = forced vital capacity; % predicted = percent of the predicted value; TL,CO = transfer factor for carbon monoxide of the lungs; PImax = maximal inspiratory mouth pressure; QPT = quadriceps peak torque; 6 MWD = 6-min walking distance; $n = 29$ outpatients with sarcoidosis for vitality and depression.

*$p = 0.0025$.

middle-aged men, without changes in median circulating FSH and LH concentrations; and (2) a statistically significant worse respiratory and skeletal muscle function, functional exercise intolerance, diminished vitality and depressed mood were not related to the reduced circulating (free) testosterone concentrations in male outpatients with sarcoidosis.

Hypogonadism

Male outpatients with sarcoidosis had reduced median circulating testosterone concentrations (Table 3). Comparable findings have been found in African American outpatients with sarcoidosis.[17] Nevertheless, the present study is the first to include an age-matched control group. In addition, all except one patient were of white ethnic origin.

In the present study, 14 patients (46.7%) had circulating testosterone concentrations below the lower limit of normal (⩽300 ng/dl).[15] Subsequently, a compensatory reduction in circulating SHBG concentrations in the patients ($p = 0.0515$, Table 3) has been found to increase the circulating free testosterone concentrations. The number of patients ($n = 7$, 23.3%) with low circulating free testosterone concentrations (⩽5 ng/dl)[15] was lower than the number of patients with low circulating testosterone concentrations. However, patients' median circulating free testosterone concentrations still remained below the values of the healthy control subjects (Table 3).

Median circulating testosterone concentrations were not different between patients who used oral corticosteroids and those who did not. This is in line with previous findings in patients with sarcoidosis[17] or chronic obstructive pulmonary disease (14;19). Median circulating testosterone concentrations were still significantly lower as compared to healthy control subjects after excluding four patients with self-reported co-existing comorbidities. In addition, circulating testosterone concentrations were not related to the number of pack years or circulating CRP concentrations (Table 4). Therefore, other factors may have contributed to the presence of hypogonadism in male outpatients with sarcoidosis. Indeed, absent increases in circulating levels of FSH (<8.1 mUI/ml)[15] and LH (<5.3 mUI/ml)[15] have been found in 12 (85.7%) and 13 (92.9%) out of 14 hypogonadal outpatients with sarcoidosis, respectively. These findings point strongly towards a hypofunctioning of the hypothalamus–pituitary–gonadal axis in male outpatients with sarcoidosis.[18] In fact, Adler and colleagues reported also hypogonadotrophic-hypogonadism in 85.7% of the hypogonadal male outpatients with sarcoidosis.[17] However, a hypofunctioning of the hypothalamus–pituitary–gonadal axis in combination with a primary testicular dysfunction[18] cannot be excluded based on earlier[17] or current results.

Quadriceps muscle function

Recently, the present authors hypothesized that physical deconditioning, at least in part, can be responsible for quadriceps muscle weakness in sarcoidosis.[3] The lack of a significant relationship between reduced circulating (free) testosterone concentrations and quadriceps muscle weakness in male outpatients with sarcoidosis (even after controlling for age, body weight and height) is in favor of this hypothesis. In fact, the relationship between quadriceps muscle weakness and hypogonadism does not appear to be straightforward,[33] whereas its relationship with physical inactivity is well established.[34]

Recently, the possible underlying factors of a reduced muscle function in patients with sarcoidosis have been discussed in depth.[35] To date, the presence of the disease in skeletal muscles of patients with sarcoidosis cannot be ruled out.[36] In addition, effects of oral corticosteroids on muscle function may not be underestimated. Previously, a significant inverse relationship has been found between the mean daily dose of oral corticosteroids and quadriceps peak torque in the patients who received oral corticosteroids in the 6-month period preceding the tests.[3] In addition, an a posteriori analysis of variance revealed a worse quadriceps muscle function in male outpatients with sarcoidosis who used oral corticosteroids in the past 6 months as compared to those who did not and healthy middle-aged control subjects (upper left panel of Figure 2). Noteworthy, patients who did not use oral corticosteroids were still significantly weaker as compared to healthy control subjects. Additionally, similar findings were found for the 6-min walking distance (lower left panel of Figure 2).

Respiratory muscle function

Weakened inspiratory muscles[3,6,37] may contribute substantially to the sensation of dyspnea during day-to-day activities in outpatients with sarcoidosis. In fact, reduced maximal inspiratory mouth pressure has been related to worse scores for dyspnea on the modified British Medical

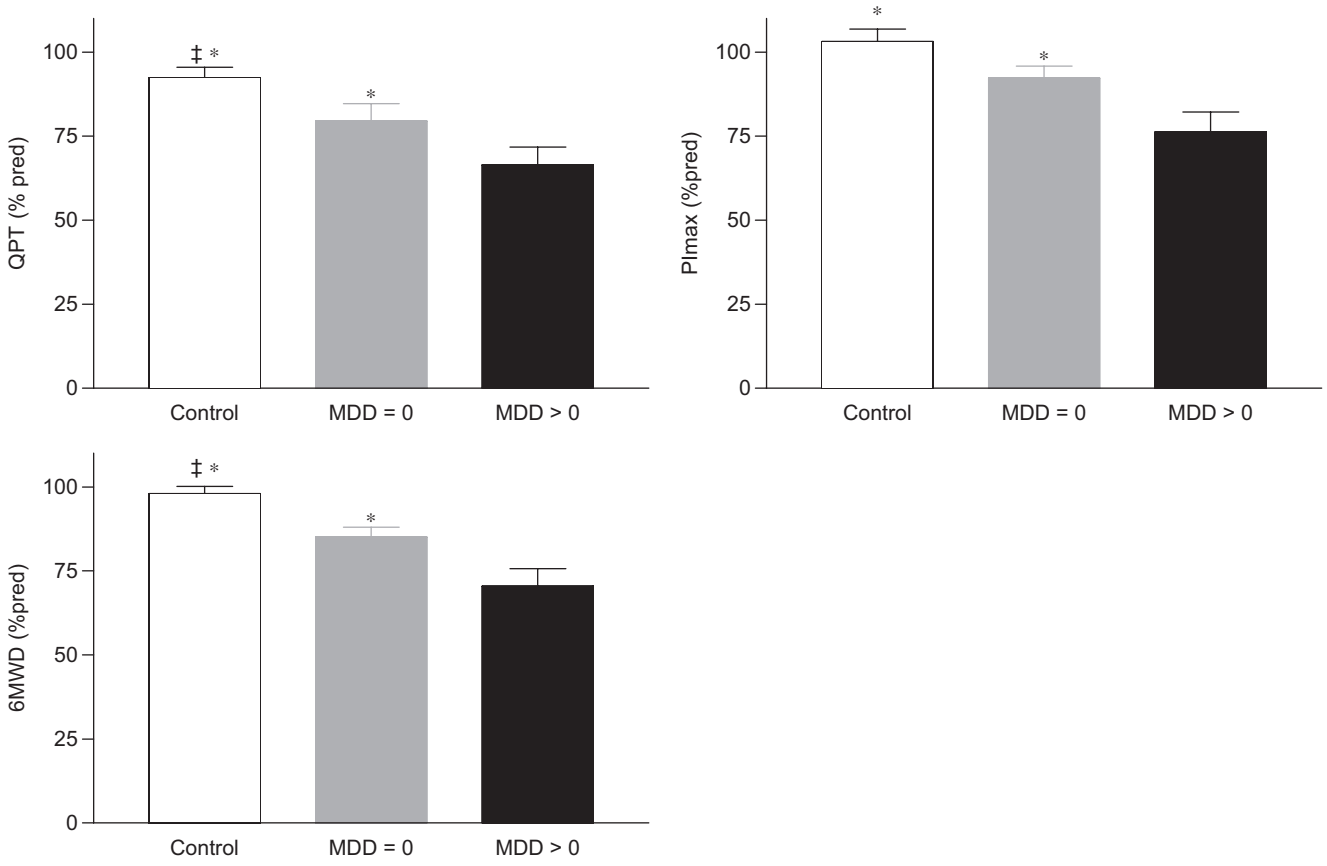

Figure. 2 *Upper left panel*: Mean (SE) quadriceps peak torque (QPT, expressed as a % of the predicted value) of healthy control subjects, outpatients with sarcoidosis who did not use oral corticosteroids in the past 6 months (MDD = 0), and outpatients with sarcoidosis with a mean daily dose of corticosteroids of 4 mg per day (IQR: 2–12) in the past 6 months (MDD > 0). *:$p<0.05$ versus MDD > 0; ‡:$p<0.05$ versus MDD = 0. *Lower left panel*: Mean (SE) 6-min walking distance (6MWD, expressed as a % of the predicted value) of healthy control subjects, outpatients with sarcoidosis who did not use oral corticosteroids in the past 6 months (MDD = 0), and outpatients with sarcoidosis with a mean daily dose of corticosteroids of 4 mg per day (IQR: 2–12) in the past 6 months (MDD > 0). *:$p<0.05$ versus MDD > 0; ‡:$p<0.05$ versus MDD = 0. *Upper right panel*: Mean (SE) maximal inspiratory mouth pressure (PImax, expressed as a % of the predicted value) of healthy control subjects, outpatients with sarcoidosis who did not use oral corticosteroids in the past 6 months (MDD = 0), and outpatients with sarcoidosis with a mean daily dose of corticosteroids of 4 mg per day (IQR: 2–12) in the past 6 months (MDD > 0). *:$p<0.05$ versus MDD > 0.

Research Council scale.[37] Moreover, decreased respiratory muscle endurance time has been shown to be inversely related to subscales *mobility* and *body movement* of the Sickness Impact Profile in outpatients with sarcoidosis, irrespective of the pulmonary function impairment.[6]

To date, the underlying causes of respiratory muscle weakness in male outpatients with sarcoidosis remain unknown. Indeed, a statistically significant reduction in inspiratory muscle strength did not appear to be caused by a hypogonadal status (Table 4), disuse or systemic inflammation.[3] Moreover, oral corticosteroids did not appear to affect maximal inspiratory mouth pressure.[3,6,38] Then again, the mean daily dose of oral corticosteroids has been shown to be independently responsible for 32% and 54% of the variance in maximal inspiratory mouth pressure in patients with chronic obstructive pulmonary disease[27] or cystic fibrosis,[39] respectively. In the present study, an a posteriori analysis of variance showed only a worse inspiratory mouth pressure in the patients who used oral corticosteroids in the past 6 months compared to those who did not and healthy middle-aged control subjects (upper right panel of Figure 2).

Measurement of maximal inspiratory mouth pressure is by far the most widely used test for assessing the inspiratory muscle strength.[40] In fact, the mean PImax sustained for 1 s (84.8% of predicted) was statistically significant worse compared to healthy age-matched control subjects (Table 2) and has been shown to be comparable to recent results of Kabitz and colleagues (85.6% of predicted).[2] Nevertheless, the latter authors have not found a statistically significant difference between nonvolitional inspiratory muscle strength between patients with sarcoidosis and healthy control subjects.[2] This may imply that on average inspiratory muscle strength is not different using effort-independent techniques. Unfortunately, the present authors did not have access to a magnetic stimulator at the time of the present study.

Vitality and depression

Diminished vitality and increased depression have been reported in patients with sarcoidosis compared to healthy peers[3,7–10]. These persistent clinical complaints may, at least in part, be explained by a hypogonadal status.[11,12–14,16,41] Nonetheless, reduced circulating (free) testosterone concentrations were not related to diminished vitality and depressed mood in the present male outpatients with sarcoidosis (Figure 1 and Table 3). Other underlying factors (i.e. physical deconditioning) may therefore be partially responsible for the reduced vitality and increased depression in sarcoidosis.[3] Actually, the involvement of physical deconditioning in diminished vitality and depressed mood scores may be indicated by the significant improvement in scores following an exercise-training program in outpatients with sarcoidosis.[42–44] This, however, has never been studied in sarcoidosis.

Methodological and statistical considerations

The present study has clear limitations. Only circulating CRP concentrations have been studied as a marker of systemic inflammation, while specific pro-inflammatory cytokines are thought to play a role in the development and/or maintenance of hypogonadism.[45] Nevertheless, circulating levels of interleukin-6, interleukin-8, tumor necrosis factor alpha and its soluble receptors were not or only weakly related to the reduced circulating (free) testosterone concentrations in male outpatients with clinically stable but advanced chronic obstructive pulmonary disease.[15,46] Whether and to what extent systemic markers of disease severity (e.g. serum levels of soluble interleukin-2 receptor, angiotensin converting enzyme and neopterin) may somehow be partially related to hypogonadism in male sarcoidosis patients remains currently unknown.[47,48]

The presence of sarcoidosis at the scrotum and/or pituitary gland has not been ruled out and may therefore, at least in part, be responsible for the observed hypogonadism in male outpatients with sarcoidosis.[49] Nevertheless, none of the patients complained spontaneously about recurrent fainting or dysesthesia[50] at the time of the study. Additionally, these types of sarcoidosis are very rare.[51,52]

Only male subjects have been studied in the present study, which appears to be understandable. Then again, it may be meaningful to perform a similar study in female sarcoidosis outpatients.[53]

The external validity of the present findings is limited to male outpatients with sarcoidosis of white ethnic origin[54] and should therefore be reproduced in a larger sample with ethnically diverse sarcoidosis patients.[55] Indeed, the present results are rather hypotheses generating than definitive.

The present sample may have been too small to find significant differences in median circulating testosterone concentrations between patients who had been using oral corticosteroids (284 ng/dl) and those who did not (345 ng/dl, $p = 0.8843$). Then again, median circulating free testosterone concentrations were identical (7.32 ng/dl). In addition, Adler and colleagues also did not find an effect of oral corticosteroids on gonadal status in male patients with sarcoidosis.[17]

Statistically significant differences between groups need to be interpreted in the light of the number of comparisons that were made in the present study. Nonetheless, the current statistical procedures have been used to test predefined hypotheses. Moreover, '*Bonferoni adjustments are at best, unnecessary and, at worst, deleterious to sound statistical inference*'.[56] Finally, due to the cross-sectional design, it is impossible to work out the temporal sequence of the present clinical outcomes.[57]

Future directions

To date, the clinical relevance of hypogonadism in male outpatients with sarcoidosis remains unknown. In particular, a lack of significant relationships with the current clinical outcomes raises questions. It may therefore be too early to consider randomized controlled trials on the effects of testosterone supplements in highly selected hypogonadal male outpatients with sarcoidosis. Then again, hypogonadism can be one of the underlying factors causing erectile dysfunction in middle-aged men[58] and may therefore be worthwhile to study in future studies in middle-aged male patients with sarcoidosis. Unfortunately, erectile dysfunction has not been included as an outcome in the present study. In fact, erectile dysfunction in sarcoidosis has only been reported in several case-reports of patients with neurosarcoidosis or with sarcoidosis in the scrotum.[50,59,60]

Conclusions

A worse respiratory and quadriceps femoris muscle function, exercise intolerance, diminished vitality and depressed mood were not related to the hypogonadal status in men with sarcoidosis. Therefore, the clinical relevance of hypogonadism warrants further studies in men with sarcoidosis. Nevertheless, physicians still have to be aware that hypogonadism can be one of the underlying causes of one of the aforementioned clinical symptoms in individual male patients with sarcoidosis. Finally, oral corticosteroids may, at least in part, affect inspiratory muscle force, quadriceps muscle force and 6-min walking distance in male outpatients with sarcoidosis.

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Conflict of interest statement

None of the authors have a conflict of interest to declare in relation to this work under this sub-heading.

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